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Gastrointestinal and Metabolic Problems Associated With Immunosuppression With Either CyA or FK 506 in Liver Transplantation

D.H. Van Thiel, **M. Iqbal**, **A. Jain**, **J. Fung**, **S. Todo**, and **T.E. Starzl**
Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, Pittsburgh, PA

Since its introduction in 1979, CyA has been the immunosuppression agent of choice in clinical transplantation of all solid organs.1 More recently, a novel new immunosuppressive agent, FK 506, has been introduced in experimental transplantation.2 Most recently, it also has been introduced into clinical liver transplantation. Both agents appear to be T cell-specific and induce their immunosuppressive effects by impairing interleukin-2 production and receptor expression.[3] Presumably, CyA initiates its immunosuppressive actions by an intracellular protein (receptor), cyclophillin, and by interacting with one or more calcium-binding proteins.[4] In contrast, FK 506 appears to bind to a completely different intracellular protein, putatively called fugiphillin. Because these two drugs act via different binding proteins, and presumably follow different intermediate steps to produce T cell suppression, we have compared the two in terms of their untoward gastrointestinal and metabolic effects in liver transplant patients.

METHODS

Subjects

The first 20 patients receiving a primary liver graft with FK 506 immunosuppression were matched for age (in all but two cases), gender, primary liver disease diagnosis, and United Network Organ Sharing (UNOS) score with a patient receiving a primary liver graft under CyA immunotherapy at the same institution during the preceding 2 years. Each FK 506 subject, with two exceptions, was matched for age within 5 years with a control and identically for all other characteristics identified above (gender, liver disease, UNOS score).

Assays

Pretransplant levels of serum uric acid, cholesterol, and amylase, as well as fasting blood sugar were determined on all subjects.

Every patient transplanted under FK 506 immunosuppression had each measurement repeated at 10 days and again 15–20 days posttransplantation. When available, similar data for the controls transplanted under CyA were obtained from the medical records at approximately similar time points following liver transplantation.

Symptom Survey

Each patient treated with FK 506 was seen daily from day 1 postoperatively through day 20 and assessed for the presence of each of the signs or symptoms listed in Table 1. Whenever any gastrointestinal symptoms are identified posttransplantation, upper gastrointestinal

Address reprint requests to D.H. Van Thiel, MD, 3601 Fifth Avenue, Falk 5C, Pittsburgh, PA 15261.

panendoscopy with biopsy of the duodenum and gastric antrum was performed. Endoscopy had been performed preoperatively on all subjects (both FK 506 and CyA-treated patients), and the endoscopic and biopsy findings found postoperatively were compared both between groups and for pre- and post-liver transplantation changes. For this purpose, two endoscopic biopsies from the duodenum and two from the gastric antrum were fixed overnight in 10% buffered formalin, sectioned at 5 μm, stained with hematoxylin and eosin, and reviewed by staff pathologists at the Presbyterian-University Hospital, Pittsburgh, PA.

The charts of the 20 controls treated with CyA were reviewed retrospectively for evidence of any of the 16 signs and symptoms assessed prospectively and daily in the FK 506-treated patients.

All values are reported as means ± SEM. Significant differences between groups were determined using either the student's *t* test (two-tailed) or χ^2 analysis. A *P* value of <0.05 was considered to be significant.

RESULTS

The age, gender, liver disease diagnosis, and UNOS score for each FK 506- and CyA-treated patient are shown in Table 2. As noted in this table, each FK 506- and CyA-treated patient was identically matched for gender, primary liver disease, and UNOS score. An attempt was made to match each FK 506 patient with a CyA-treated patient of the same age ± 5 years, and this was possible with all but two patients (nos. 4 and 10). As a result, no significant difference for age was seen between the two groups. As evidenced by the UNOS scores, both real number and the mean value, these patients were all quite ill and would have been candidates for liver transplantation at any center in the world.

The mean pre- and post-liver transplantation serum levels of uric acid, cholesterol, and amylase, and the fasting blood sugar levels for each patient are shown in Table 3. The serum uric acid levels increased significantly in both groups when pre- and post-liver transplantation values were compared. No difference between groups for pre- and post-liver transplantation uric acid values was evident.

The serum cholesterol level declined significantly ($P = 0.037$) in the FK 506-treated group and increased arithmetically but not significantly in the CyA-treated group. As a result, a highly significant difference ($P = 0.015$) between groups was evident for the post-liver transplantation cholesterol levels, whereas no difference existed in the pre-liver transplantation values.

The serum amylase values did not differ significantly pre-liver transplantation and decreased post-liver transplantation in both groups. In neither group was the reduction statistically significant, but the post-liver transplantation level in the FK 506-treated group was significantly less ($P = 0.048$) than that of the CyA-treated group.

The fasting blood sugar levels did not differ within and between groups pre- and post-liver transplantation. For each group, an arithmetic but insignificant increase was noted following transplantation. These differences are not biologically significant.

Abdominal computed tomography (CT) scans were available in all patients studied preoperatively and in the majority of patients studied postoperatively. No evidence for pancreatic inflammatory disease was evident in either group before or after liver transplantation.

The two groups differed for only two of the 16 signs and symptoms assessed. The FK 506 group experienced vomiting ($P = 0.026$) while the CyA-treated group experienced more

abdominal pain ($P = 0.023$). When all 16 symptoms and signs of potential adverse reaction were pooled, no difference between the two groups was evident.

Thirteen of the CyA-treated controls had abdominal CT scans both before and after liver transplantation. No evidence of pancreatic disease developed in any of these controls as a consequence of transplantation. Six of the FK 506-treated patients had abdominal CT scans obtained both pre- and post-liver transplantation. Again, no change in the appearance of the pancreas was evident between these two studies.

CT scans of the head were obtained for four CyA-treated patients and four FK 506-treated patients. Small to moderate volume loss was seen pre- and post-liver transplantation in two of the individuals transplanted for alcoholic liver disease. No abnormalities not present pretransplantation developed in either group posttransplantation.

DISCUSSION

The data obtained in highly matched patients undergoing primary liver transplantation with either standard CyA or FK 506 immunosuppression demonstrate several important findings relative to the long-term use of both immunosuppressive agents.[4]

First, both agents result in a moderate, albeit not clinically important, increase in serum uric acid levels (Table 3). The increase following liver transplantation was greater arithmetically but not statistically in the FK 506-treated group. It is well-established that CyA has a variety of nephrotoxic actions, one of which is to impair uric acid excretion, resulting in an increase in the serum uric acid level and the potential for clinical uric acid arthropathy and nephropathy.[5] It appears from these data that FK 506 may do the same. It remains to be shown, however, whether the increase in uric acid levels in the FK 506-treated patients is the result of increased production or reduced excretion rate. The latter mechanism would appear more likely, but no data are currently available to distinguish between these two possibilities.

Second, CyA is known to enhance the production of cholesterol as a result of up-regulation of the rate-limiting enzyme involved in cholesterol biosynthesis, HMG-Co-a reductase.[6] Moreover, CyA increases plasma levels of low density lipoproteins and apolipoprotein B. Both mechanisms result in about a 30% increase in serum cholesterol levels with prolonged use of CyA. The present data demonstrate a CyA-associated arithmetic increase in serum cholesterol, and a significant FK 506 reduction in serum cholesterol between pre- and post-liver transplantation values (Table 3). This difference between the two drugs may have very important implications for the long-term survival of both patients and grafts, as a result of atherosclerosis and chronic rejection, as occurs as a result of foam cell obliteration of vascular lumina. At present, no such statement can be made, but, should this difference in cholesterol levels persist with a longer experience with FK 506, this finding should enhance the acceptability of FK 506 as the agent of choice for chronic immunosuppression, should all other factors be equal.

Third, despite the preliminary experience in animals, that FK 506 can produce a patchy pancreatic acinar necrosis and vasculitis which clinically might be termed a drug-induced form of pancreatitis, no evidence for pancreatitis was seen in either patient group studied.[7–9] Specifically, the serum amylase declined in both groups postoperatively, with the decline being greater in the FK 506-treated group than in the CyA-treated patients. Moreover, neither group showed a significant alteration in the level of fasting blood sugar or pancreatic morphology assessed by abdominal CT scanning obtained pre- and post-liver transplantation. Thus, despite the worrisome experience in animals, the present early experience with FK 506 in humans does not support the observation that FK 506 is a pancreatic toxic drug.

Finally, although both drugs have been associated with a wide spectrum of transient abdominal and neurologic signs and symptoms, little or no difference was seen for 16 common signs and symptoms experienced by transplant recipients and thought to be a result of the immunosuppressive agents used to control or prevent rejection (Table 1).

Transient vomiting appeared more commonly in patients treated with FK 506 ($P = 0.026$), while transient abdominal pain occurred more often in those on CyA ($P = 0.023$). The clinical significance of these findings is uncertain, as both were transient, no specific abnormality could be identified as the cause for either of these two complaints, and no specific therapy appeared to alleviate them. In both groups, they appeared as minor inconveniences rather than as problems that necessitated a change in therapy or other action. This experience differs considerably from the experience in experimental animals, such as the dog and rat.[7–13] The relative absence of abnormalities found following liver transplantation on endoscopy of the upper gastro-intestinal tract and the histologic findings found in the gastric antrum and duodenum of the two groups of subjects studied were surprising.

In summary, the preliminary short-term experience with FK 506 suggests that FK 506 compares well with CyA as the primary immunosuppressive agent used in a liver transplant population. The reduction in serum cholesterol seen with FK 506, as opposed to CyA, may be an advantage with a longer experience. Both agents appeared to increase serum uric acid levels and neither adversely affected pancreatic function, as assessed in this preliminary investigation.

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Table 1

Symptom Survey Utilized

Gastrointestinal Items	Neurologic Items
Nausea	Headache
Vomiting	Dizziness
Retching	Tremor
Abdominal pain	Seizure
Abdominal cramps	Psychosis
Diarrhea	Toxic encephalopathy
Incontinence, stool	Tingling
Incontinence, urine	Numbness

Table 2

Characteristics of the Two Groups of Subjects Studied

FK 506 Patients	Gender	Age	Liver Disease Diagnosis*	UNOS Score	Age*
1	M	31	PSC	2	35
2	M	18	Alagille's	1	18
3	M	38	PNC-NANB	3	35
4	M	19	PSC	3	28
5	M	43	PNC-C	1	45
6	M	38	PNC-NANB	4	43
7	M	42	PNC-ETOH	1	46
8	M	39	PNC-ETOH	4	40
9	F	41	PNC-B	2	36
10	F	49	Budd-Chiari	4	25
11	M	49	PSC	2	45
12	M	28	Caroli's	2	24
13	F	41	PBC	2	44
14	F	55	PBC	2	55
15	F	37	PNC-ETOH	3	33
16	M	55	PNC-ETOH	3	58
17	M	41	PNC-ETOH	3	44
18	F	33	PBC	1	42
19	F	64	PNC-C	2	64
20	F	43	PNC-ETOH	2	41
Mean ± SEM		40.2 ± 2.5		2.5 ± 0.2	40.1 ± 2.6

Abbreviations: PSC, primary sclerosing cholangitis; PNC-NANB, post-necrotic cirrhosis due to putative NANB; PNC-C, cryptogenic post-necrotic cirrhosis; PNC-ETOH, alcoholic cirrhosis; PNC-B, post-necrotic cirrhosis due to hepatitis B virus; PBC, primary biliary cirrhosis.

*Age of matched CyA control patients.

Table 3

Serum Uric Acid, Cholesterol, Amylase, and Fasting Blood Sugar Before and After Liver Transplantation in the Patients Studied

Parameter	Group	Pretransplantation	Posttransplantation	*P* Value
Uric acid (mg/dl)	FK 506	4.5 ± 0.4*	7.8 ± 1.0†	0.007
	CyA	4.2 ± 0.5	6.2 ± 0.9	0.063
Cholesterol (mg/dl)	FK 506	200.5 ± 37.3	123.7 ± 9.2‡	0.037
	CyA	148.5 ± 25.0	168.5 ± 5.6	0.382
Amylase (IU/L)	FK 506	163 ± 86	53 ± 5‡	0.222
	CyA	108 ± 13	79 ± 12	0.079
Fasting blood sugar (mg/dl)	FK 506	107 ± 8.0	137 ± 19	0.110
	CyA	127 ± 12.0	134 ± 19	0.644

*Not significantly different from the pretransplantation level in the CyA-treated group.

†Not significantly different from the posttransplantation level in the CyA-treated group.

‡Significantly different from the value for the CyA-treated group at the same time in relation to the liver transplantation.